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ABSTRACTS OF PAPERS AND DISCUSSION

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RESIDENTS' MEETING

*Staining Properties of Russell Bodies in Plasmocytes and Crystals in a Lympho-plasmocyte in Comparison with Amyloids**

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(Sponsor: Alfred Angrist)

This study was made to characterize intracytoplasmic crystals in a lympho-plasmocytoid cell found in bone marrow, lymph nodes and peripheral blood in a case of an unusual lymphomatous disease**. The patient was a 60 year old woman with an obscure progressive wasting disease characterized by generalized lymphadenopathy, moderate hepatosplenomegaly and a neuromuscular disorder. She also had a duodenal ulcer and hyperthyroidism.

A biopsy of a lymph node made in 1956 showed the pattern of a lymphoma, with proliferation of lymphocytoid cells and mononuclear reticulum cells. Many crystal cells were present. The review of another biopsy removed in 1951 showed massive proliferation of epithelioid cells resembling a sarcoid reaction and some of the crystal cells, as well as eosinophils.

Various staining methods were applied to formalin-fixed paraffin sections. Tissues containing plasmocytes with Russell bodies and blocks exhibiting "primary," "secondary" and senile cardiac amyloids were used for comparison with lymph nodes containing crystal cells.

The apparent isoelectric points of the crystals, Russell bodies and amyloids were determined by the method of Singer and Morrison[1]. Sections were stained overnight in aqueous solutions of eosin (10^{-4}M) or methylene blue (2×10^{-4}M) at intervals of about one pH unit over the range of pH 3.0 to 9.5. The cross-over zone of the curves for basophilia and acidophilia was taken as the isoelectric point.

Crystals and Russell bodies in different cells exhibited an isoelectric range, pH 6.0 to 7.5. This is the range exhibited by human gamma globulin[2]. A sample of Fraction II (Mann Research Laboratory), fixed in formalin and sectioned in paraffin, gave the same range. Such a result is entirely compatible with the accumulated evidence for the production of gamma globulin by plasmocytes[3]. Apparently the crystals present in the lymphoplasmocyte described consisted of the same or a closely-related protein, in a different physical state.

By contrast, all specimens of amyloid studied exhibited a fairly sharp isoelectric

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** This was a patient at the Mt. Sinai Hospital, New York, admitted July, 1956. A description of the case is being prepared by A.F.G.

point, at about pH 5.0. The plasma proteins having comparable isoelectric points are the alpha and beta$_1$ globulins[2] and associated mucopolysaccharides. In extraction studies it has been shown that amyloids migrate electrophoretically like such globulins[4]. Furthermore, there is frequently an elevated alpha (or occasionally beta) globulin fraction in the serum of patients with amyloidosis. These observations lend support to the concept that tissue amyloid may be formed by excessive amounts of circulating globulins and mucopolysaccharides that deposit locally.

Additional staining methods were applied. All of the objects were PAS-positive. This property is compatible with the known carbohydrate content of the various plasma globulins mentioned, as well as of the mucopolysaccharides associated with globulins in amyloid. The amyloids stained positively by the Congo red and crystal violet methods. The Russell bodies and crystals did not. Formalin-fixed smears or frozen sections stained with either Sudan black B or oil red O showed no dye uptake by either Russell bodies or crystals. Yet both objects stained with the Baker acid-hematin method, even after pyridine extraction, as did gamma globulin. Although these results suggest that stainability is not attributable to a phosphatide, no possible cause is known.

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DISCUSSION

NORMAN S. COOPER: I should like to ask Dr. Goldberg whether he tested serum albumin for its isoelectric range by this same technique, and what range it fell in.

ARTHUR F. GOLDBERG: We never tested serum albumin.

CHANDLER A. STETSON, JR.: I should like to ask whether the patient who had these cells containing crystals had a cryoglobulin, or other abnormality of plasma proteins.

ARTHUR F. GOLDBERG: We did not test for cryoglobulins at that time. The patient had an abnormal electrophoretic pattern. A sharp peak was present in the gamma globulin range, but the total amount of gamma globulin was not elevated.

Localization with Fluorescent Antibodies of Complement Fixed in Altered Glomeruli

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With the use of immunohistologic techniques it is possible to demonstrate rabbit antibody globulin in the glomeruli of rats injected with rabbit anti-rat kidney serum[1]. Specific apple-green fluorescence is emitted from the glomerular capillary basement membranes, the sites of supposed *in vivo* localization of anti-kidney antibody that *in vitro* take up the labeled anti-rabbit globulin. Lange demonstrated that serum lost its hemolytic complement when perfused through kidneys previously exposed to nephrotoxic serum[2]. He concluded that complement was fixed in the tissue by antibody-antigen aggregates. Immunohistologic demonstration of complement fixed in tissues at sites of antibody globulin localization would provide more conclusive evidence of specific antibody-antigen aggregation and evidence of complement fixation to these aggregates.

Immune serum against guinea pig, human, or rat complement can be produced by the injection of rabbits with a special immune aggregate (SAC′) composed of sensitized sheep red cell stromata (SA) exposed to complement (C′)[3]. This immune serum, when absorbed with a sufficient quantity of sensitized stromata (SA), agglutinates specifically sensitized cells exposed to fresh complement (EAC′), and does not agglutinate sensitized cells exposed to complement inactivated by heat or a chelating agent. Precipitins in this absorbed anti-complement serum are also demonstrable against fresh serum (C′) by capillary and agar gel diffusion methods. The immune serum when conjugated with fluorescein isothiocyanate will also coat presensitized cells (EAC′).

Sections of kidneys from rats that were injected with rabbit anti-rat kidney serum 15 minutes, 4 hours, and 10 days prior to sacrifice have been exposed to guinea pig serum. It has been shown that guinea pig complement is fixed in the same glomerular sites at which nephrotoxic rabbit globulin is localized. The cut sections of kidney are first exposed to fresh guinea pig serum diluted 1/30, then rinsed and finally exposed to anti-guinea pig complement immune serum conjugated with fluorescein isothiocyanate. Specific apple green fluorescence is emitted from the glomerular capillary membranes[4]. No fluorescence is emitted by kidney sections in the following control situations: 1) sections from normal rats or sections from rats injected with normal rabbit serum, exposed first to complement and then to the conjugated anti-complement serum; 2) nephrotoxic kidney sections exposed first to heated or chelated complement and then to conjugated anti-complement serum; 3) nephrotoxic kidney sections exposed to anti-complement serum alone; and 4) sections exposed to guinea pig complement, then to non-conjugated anti-guinea pig complement serum, and finally to conjugated anti-guinea pig complement, the findings indicating that non-conjugated antibodies have blocked the uptake of conjugated anti-complement antibodies.

It is possible to demonstrate the *in vivo* fixation of rat complement in experimental nephrotoxic nephritis, using these same techniques. The nature of the mechanisms involved in the action of rat complement and other rat serum components in nephrotoxic nephritis is subject to variable interpretations and is the object of studies now in progress. Application of the principles and methods utilized in this study is also being made in search for complement fixed in lesions of tissue obtained at biopsy and postmortem in humans with diseases that may involve pathological immune processes.

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DISCUSSION

JOHN G. KIDD: Dr. Murphy, I believe, is in the audience. Does he have any comments to make on this work?

GEORGE E. MURPHY: I believe the evidence, here presented, that guinea pig complement is fixed in glomeruli in rats injected with nephrotoxic serum speaks for itself.

JOHN G. KIDD: I should like to ask Dr. Burkholder whether he can distinguish between human antibody globulin and human complement in the kidney of a person with naturally occurring glomerulonephritis.

PETER M. BURKHOLDER: That is a very good question that can also be applied to the problem of distinguishing between rat globulin and rat complement fixed in the glomeruli of rats with nephrotoxic nephritis. In the course of experimental nephritis, rat globulin, as well as rat complement, is probably localized at the glomerular sites of rabbit anti-rat kidney globulin in aggregation with glomerular antigen. The problem then is to distinguish between fixed rat complement and fixed rat globulin, since complement and globulin are antigenically related, that is, they have cross-reacting antigenic determinants. Studies utilizing coated red cells and hemagglutination technique show that anti-globulin agglutinates cells coated with complement as well as cells coated with globulin, and anti-complement agglutinates cells coated with globulin as well as cells coated with complement. When one examines kidney sections from humans with glomerulonephritis, it is to be expected that anti-complement immune serum which agglutinates cells coated with human globulin will, when conjugated with fluorescein isothiocyanate, localize in sites of human globulin as well as in the sites of human complement in the tissues. Presumably, these two serum components would localize at the same sites. Because of this problem of cross reaction of anti-complement with globulin in the demonstration of homologous complement fixed *in vivo*, we at present utilize fixation of heterologous complement, as classically done in complement fixation *in vitro*, for the demonstration of antibody-antigen aggregates in the tissues.

JOHN G. KIDD: How different are your anti-complement and anti-globulin serums?

PETER M. BURKHOLDER: The titers of agglutinins in the cross reactions are generally considerably lower than the titers of specific agglutinins. Anti-guinea pig complement, for instance, has a titer of agglutinins against cells coated with guinea pig complement of some eight times that of the titer of agglutinins against cells coated with guinea pig globulin. Anti-guinea pig globulin, however, agglutinates cells coated with guinea pig globulin and cells coated with guinea pig complement in about the same titer. The same is, in general, true with immune serum against human complement. Though the titer of specific antibodies against human complement is higher in anti-human complement immune serum than the titer of antibodies against human globulin, it is still impossible, from a practical standpoint, to obtain an immune serum against complement that does not possess any antibodies against other serum globulins.

STEPHEN S. STERNBERG: I think this question is a little bit beside the point, but will you tell us the mechanism of action of the chelating agent? How does this inactivate the complement?

PETER M. BURKHOLDER: EDTA was the chelating agent used in our experiments. Its mechanism of action is the binding of divalent cations, such as calcium and

magnesium, that are required for the action of complement to immune aggregates. The components of complement fix or act upon sensitized cells in the sequence of C'1, C'4, C'2, and C'3. Calcium is required for the fixation of the first component of complement and magnesium for the action of the second component. By removing these divalent cations one prevents the action of complement upon the immune aggregate.

HELEN WENDLER DEANE: I wondered why you stated that these antigens or antibodies, or both, were in the basement membrane. It looked suspiciously to me as though they might be in Bowman's epithelium rather than in the basement membrane.

PETER M. BURKHOLDER: The sections are not as thin as we would like. Our microtome is set to cut sections at 2.5 microns and occasionally it delivers sections up to 5 microns in thickness. Thick sections are sometimes difficult to interpret with the resolution obtained in fluorescence microscopy. Thin, delicate structures are thickened and blurred or appear to be encroached upon by brightly fluorescing neighboring structures. We observe fluorescence to occur at the site of the glomerular capillary basement membrane. The localization may be to one side or the other of the membrane, but in general it follows the contour of the membrane, so that in the glomeruli of the rats a delicate thin fluorescent membrane is observed. In studying some sections of human kidney exposed to fluorescein-conjugated sera, I often see a globular pattern of fluorescence that appears to involve thickened basement membrane, but which also appears focally to involve structures contiguous with the glomerular basement membrane. I think a great deal of the evidence indicates that uptake of fluorescent antibodies occurs at the site of the glomerular basement membrane.

HELEN WENDLER DEANE: Dr. Marilyn Farquhar has demonstrated that protein droplets are taken up by the podocytes and this may very well be similar.

PETER M. BURKHOLDER: Yes, and Vasquez and Dixon in correlating findings of fluorescence microscopy with electron microscopy have demonstrated globules of material along the basement membranes of the glomerulus that they interpret to have the properties of globulin. Of course their model in this case is a different one, namely, nephritis produced with foreign serum.

SEYMOUR COHEN: What happens when you try to absorb your anti-complement with gamma globulin?

PETER M. BURKHOLDER: In some of our studies anti-guinea pig complement serum did react positively with nephrotoxic rat kidney sections that had not been exposed to guinea pig complement. This is interpreted as a cross reaction of anti-guinea pig complement with rat complement. It is possible to obviate this cross reaction by absorbing the conjugated anti-guinea pig complement with serum homologous to the animal whose tissues are being examined. With reference to your proposal of absorbing anti-human complement with human globulin or anti-rat complement with rat globulin, I feel that most of the antibodies against complement would be lost. Apparently some of the components of complement can be isolated electrophoretically in the slower moving globulin fractions and would therefore probably be present in the globulin fraction used for the absorption. Because of this, and because of the antigenic similarities of complement and globulin, absorption of anti-complement with globulin would probably deprive the immune serum of the antibodies against complement.

Accelerated Reactivity to Bacterial Endotoxins

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Skin tests with bacterial endotoxins in normal rabbits ordinarily produce delayed inflammatory reactions which are not grossly visible for several hours and are fully developed only after a day or more. Recent chance observations indicate that rabbits with prior exposure to endotoxins show a profound modification in cutaneous reactivity to subsequent skin tests with endotoxins. The inflammatory reactions evoked were no longer delayed and mild but accelerated and intense. These Arthus-like lesions were clearly visible within an hour and well developed by six hours after skin testing. The mechanism for the accelerated response appeared uniquely different from that of the classic Arthus reaction, since only one parenteral injection of endotoxin and a latency of only one day were required for the establishment of this modified reactivity. It was found that skin tests could elicit accelerated reactions as early as 16 hours and as late as 26 days after a modifying injection of endotoxin. However, skin tests with endotoxins on the second and third days after modification consistently elicited the strongest accelerated reactions. Serum from such animals was able to transfer passively the capacity to exhibit these accelerated responses. Like other endotoxin-induced phenomena, accelerated reactivity was also found to be cross-reactive, that is, one endotoxin could modify the cutaneous reactivity to other endotoxins.

The character of the accelerated lesion together with its capacity to be passively transferred suggest that this Arthus-like reaction may be mediated by circulating antibody produced in response to the modifying injection of endotoxin. However, precipitating antibodies against endotoxins were not found before the first week following stimulation, and moreover, they were serologically specific for the immunizing endotoxin. On the other hand, the antibody implicated in accelerated reactivity should exhibit cross reactions, appear within 24 hours and reach maximal titer two to three days after stimulation. Using the sensitive modified sheep erythrocyte hemolysis test as developed by Neter, an antibody with such qualitative characteristics was demonstrated. Preliminary attempts to correlate the intensity of the accelerated cutaneous reaction with the titer of cross-reacting antibody in individual animals were encouraging, but consistent results were made difficult by the lack of accurate quantitative expressions of skin reactivity and antibody levels. The significance of these findings and their implications in the Shwartzman phenomena and other effects produced by endotoxins were discussed.

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DISCUSSION

CHANDLER A. STETSON, Jr.: More people have injected more different endotoxins into more rabbits than one can possibly imagine, and I think Dr. Lee deserves a great deal of credit for his patience and perseverance in going over the old ground and in looking every hour at the skin reactions in these rabbits. A lot of the previous work on endotoxins has been phenomenological, and in this particular problem much more analytic work is needed. I think Dr. Lee should be commended for the way he has carried the analysis so far.

One point which has probably occurred to some is that the toxic portion of various endotoxin molecules may be very much the same, whatever the source, and serologic specificity may depend on the somatic polysaccharide, while the cross reactions described by Dr. Lee may be due to antigenicity of the toxic portion of the molecule.

JOHN G. KIDD: The cross-reacting antibody in the one experiment you showed persisted at the same titer throughout the period of observation. Did this antibody fall off in any of your experiments in the way the accelerated response regularly fell off?

LEUNG LEE: In other experiments fluctuations and declines in the cross-reacting antibody titer were observed with the passage of time.

IRA GREEN: At the site of the initial reaction was another reaction seen? After three or four days is there a flare at the first site?

LEUNG LEE: No.

IRA GREEN: Can you possibly relate the accelerated local phenomena to what happens in the generalized Shwartzman phenomenon?

LEUNG LEE: It is too early to relate in specific terms the accelerated reactivity in skin to other endotoxin-induced phenomena. However, the occurrence of an early non-specific immune response to endotoxins may suggest new lines of investigation in the Shwartzman reaction and other effects produced by endotoxins.

Gastro-Duodenal Metastases from Breast Cancer: An Adrenal Steroid Induced Phenomenon?

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In the past, metastases to the gastric and duodenal mucosa from breast cancer have been considered a curiosity. Recently, however, such metastases have not only become relatively frequent but also have been a source of clinical bleeding. In 1958, for example, such metastases were seen in 12 patients, 18 per cent of patients with breast cancer who came to autopsy.

Analysis of these cases indicated that the presence of this clinically manifest and sometimes fatal complication was correlated with adrenal cortical steroid therapy. The patient with carcinoma of the breast receiving adrenal steroids, who develops the signs of a bleeding ulcer, has an even chance that there will be breast carcinoma at the site of ulceration.

DISCUSSION

ARTHUR F. GOLDBERG: Were these patients receiving testosterone during the same period that they were receiving adrenal steroids?

WILLIAM H. HARTMANN: When we investigated the possible correlation to steroids we also investigated the correlation to practically every other phenomenon we could think of, and there was none. Some patients were receiving testosterone, and some were not.

IRA GREEN: Was the general degree of metastasis the same in patients who had gastro-duodenal involvement as compared to the group of non-steroid patients? In other words, did the steroid seem to cause metastases in other areas?

WILLIAM H. HARTMANN: As you may or may not know, there are reports in the literature purporting to show an increased involvement of the spleen in people who are on steroids, and our experience is the same. In our series, statistical studies of involvement, such as of the gastro-duodenal mucosa and spleen, show it is greater in those receiving adrenal steroids than in those who are not.

JOHN G. KIDD: Was there a difference in metastasis to the myocardium in the two series?

WILLIAM H. HARTMAN: I cannot answer that at present. We are now in the process of analyzing the data and slides relative to the difference in metastases in all organs.

Dystocia Due to Fetal Ascites
Report of a Case with Congenital Malformations of Liver and Lung

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Dystocia due to fetal ascites is extremely rare; paracentesis of the fetal abdomen may be necessary to complete delivery[1]. Fetal ascites, characterized by the accumulation of fluid in the peritoneal cavity during intrauterine life, must be distinguished from other forms of fluid accumulation in the fetal abdomen, such as distended urinary bladder, cysts, cystic kidneys, hydrops, and others[2]. Congenital abnormalities of liver and lung were associated with the fetal ascites in our case.

Our patient was the second child of a 23 year old white female, and the period of gestation was 37 weeks. The past history and prenatal course of the mother were noncontributory. The mother's blood type was A, Rh negative and the father's was A, Rh positive. Cord blood was O, Rh negative, Coombs test negative. Atypical antibodies could not be demonstrated in the mother's blood. Delivery by breech extraction was halted by the distended fetal abdomen; it was necessary to perform fetal abdominal paracentesis. Fetal heart sounds were audible just prior to the paracentesis; the infant was stillborn.

The placenta weighed 900 grams (normal about 400 grams); it was increased in diameter and about double the normal thickness. Microscopically the chorionic villi appeared bulky, edematous, immature, and irregularly congested. In the cord, one umbilical artery was markedly hypoplastic, with pinpoint lumen.

At necropsy the body was small (39 centimeters from crown to heel) and weighed 2350 grams. The peritoneal cavity was markedly distended (about 500 cubic centimeters of fluid had been removed by the paracentesis). Loops of small intestine were fused by chronic inflammation of the serosa, and the parietal peritoneum showed patches of chronic inflammatory thickening. The extrahepatic bile ducts and papilla of Vater were patent. The liver was markedly enlarged, icteric, and increased in consistency. On section, irregularly distributed areas of fibrosis were evident. Microscopically the lobular pattern was normal. The portal areas were markedly increased in width, due to the conversion of the peripheral portions of the lobules into a spongy fibrovascular tissue containing numerous tiny bile ducts. There were no evidences of nodular regeneration, inflammatory cell infiltrations, or parenchymal giant cells. The original portal tracts with their arteries, veins, and ducts could be clearly made out and appeared normal.

The heart was displaced to the left by a cystic lower lobe of the right lung. The displaced heart, in turn, compressed the left lung medioposteriorly. Within the cystic right lower lobe, a large branch of the right pulmonary artery communicated by direct arteriovenous continuity with a large, worm-like, anomalous pulmonary vein. The site of transition from artery to vein was abrupt and was marked by a thin, membranous, valve-like structure.

The lower lobe of the right lung was markedly enlarged. It contained one large cyst, 7 centimeters in diameter, and the remainder of the lobe was honeycombed by tiny cysts. The large cyst was filled with yellowish clear serous fluid. There were no gross evidences of direct communication of bronchi with the main cyst cavity. Microscopically this cyst was lined by ciliated columnar epithelium and terminal bronchioles opened directly into it.

The ascites is attributable to the combined effects of portal stasis associated with the structural malformation of the liver, and cardiac stasis transmitted directly to

the portal system by way of the ductus venosus. Right heart failure resulted from the extra load on the right side transmitted through the arteriovenous shunt; additional evidences of stasis were noted in the enlarged spleen, engorged intercostal and gastrointestinal vessels, and in the markedly congested hemorrhoidal veins with perineal hemorrhage.

The malformation of hepatic architecture corresponds to that described by Potter as cystic fibrosis of the liver[3]. It may be accompanied by cystic malformations in other organs[4]. A primary vascular abnormality in the liver has also been suggested[5].

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DISCUSSION

JOSEPH C. EHRLICH: One of the main problems in this case is the classification and pathogenesis of the structural changes in the liver. One may even question if the term cirrhosis is properly applied to these alterations except in the broadest sense, since there is no fundamental distortion of hepatic architecture. Because of the sharp delimitation of the anatomic changes to the paraportal zone of the hepatic lobules, one has to consider primary cholangiolitic, primary vascular, and primary peripheral hepatocellular changes as possible pathogenetic mechanisms. Sections of this liver were studied by several consultants. Their opinions were not in agreement. Dr. Edith Potter suggested the diagnosis of fibrocystic disease of the liver in a precystic stage. This form of cystic disease of the liver is usually associated with polycystic kidneys, or more rarely with cystic pancreas or cystic spleen. There were no cystic changes in any of these organs in our case. We have been unable to find a previous report of a case of combined cystic disease of liver and lung.

HANS POPPER: I was one of those who saw the slides of this case. I would agree with the diagnosis of a developmental defect rather than an inflammatory reaction of the character of cirrhosis. It is not a cystic type of malformation but can be rather compared with the microhamartomas or Meyenberg complexes except that, in the instance in question, considerable proliferation of venous and arterial vessels can be noted. It is known that in some cases of Meyenberg complexes portal hypertension is found. Most of them occur in children, but I know of one instance in an adult who bled to death from esophageal varices. I am not aware of ascites being reported, but in the specimen observed, the process seems to extend in places to the hepatic vein to produce a postsinusoidal component of portal hypertension, which is usually associated with ascites.